## Remarks

Claims 1, 15-20, and 22-25 are currently pending in this application. Claims 1, 15-20, and 22-25 remain rejected on arguments laid out in the Office Action mailed on April 21, 2008. No claims have been amended and no new claims have been added.

Applicants would first like to thank Examiner Chen for taking time to discuss the outstanding rejection with Applicant's representatives during a phone interview on July 21, 2008. In particular, the topic of enablement for the breadth of the claims was discussed. The Examiner indicated that his concern was that the claims encompass different types of tumors including ones that are not located in the brain. The Examiner indicated that he was concerned about a putative lack of evidence that chlorotoxin can be delivered to different tumors and sites with some adminsitrative routes.

Applicants respectfully request reexamination and reconsideration of the case. The rejection levied in the Office Action is addressed below.

Claims 1, 15-20 and 22-24 remain rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In particular, the Office Action takes the position that "the specification, while being enabling for delivering chlorotoxin fused to a cytotoxic moiety to neuroectodermal tumors *in vitro* or via intravenous administration or intracavity injection of brain *in vivo*, does not reasonably provide enablement for delivering a cytotoxic moiety to a neuroectodermal tumor *in vivo* by administering a pharmaceutical composition comprising a chlorotoxin fused to a cytotoxic moiety to an individual via various administration routes."

In the phone interview of July 21, 2008 the Examiner clarified that this rejection stems from his concern over the different types of tumors and routes of administration that are encompassed by the claims. The Examiner apparently feels that the full breadth of the claims is not supported by the specification and remarked that some proteins will accumulate in the liver if delivered intravenously.

Applicants again thank the Examiner for these helpful comments. Applicants appreciate the Examiner's acknowledgement that the specification is enabling for certain routes of adminstration and certain tumors.

Applicants respectfully submit, as the Examiner has acknowledged, the specification is not required under the law to provide enablement for every species encompassed by the claims.

With respect to types of tumors outside the brain that can be targeted with chlorotoxin, Applicant has presented evidence in the present application that chlorotoxin binds to tumors that are not located in the brain. See, for example, Figure 4 (pheochromocytomas, which are located in the adrenal glands near the kidney), Figure 9 (small cell lung carcinomas), and Figure 12 (Ewing's sarcoma, a bone cancer). The specification therefore demonstrates delivery to tumors outside the brain.

With respect to species in which chlorotoxin is fused to a protein, Applicants understand that the Examiner is concerned because some proteins may accumulate in the liver. Applicants respectfully submit that there is no reason to expect that a chlorotoxin-protein conjugate would necessarily accumulate in the liver. On the contrary, Applicants have presented evidence that chlorotoxin (which is itself a peptide/small protein), when fused to a cytotoxic moiety does *not* accumulate in the liver, but is taken up by cancer cells *in vivo*. See, for example, Example 17 of US Patent No. 5,905,027 (the contents of which the present application incorporates by reference in their entirety), which shows tumor-selective uptake of $^{131}$I-TM-601 (a synthesized form of chlorotoxin) in an *in vivo* animal model for glioma. Also see, for example, the declaration by Alison O'Neill, filed May 21, 2007, which describes uptake of $^{131}$I-labeled chlorotoxin in glioma cells in human patients.

The present application also provides evidence that a chlorotoxin-protein conjugate is capable of specific binding to and uptake by cancer cells. Example 23 of US Patent No. 5,905,027 shows that treating glioma cells with a chlorotoxin-GST fusion protein attached to saporin results in a signficant and selective killing of the glioma cells. Both GST (glutathione-S-transferase) and saporin are proteins; note also that in Example 23, GST was attached to saporin

via other proteins, that is, a mouse anti-GST monoclonal antibody and then a goat anti-mouse antibody conjugated to saporin.

Thus, whereas there is no evidence provided either in the specification or by the Examiner that chlorotoxin-protein fusions would not work, the evidence shows that chlorotoxin can be used to target proteins to cancer cells such that the proteins can be taken up by the cancer cells.

With respect to different routes of administration, as the Examiner has acknowledged, Applicants have shown evidence of delivery of a cytotoxic moiety using a chlorotoxin by intracranial and intravenous administration. These are two very different routes of administration, yet chlorotoxin was able to deliver a cytotoxic moiety by both routes. Furhthermore, chlorotoxin fused to a cytotoxic moiety was shown to cross the blood brain barrier, as evidenced by its ability to reach tumors in the brain when administered intravenously. The Examiner has not provided any reason that chlorotoxin would *not* be expected to deliver a cytotoxic moiety by other routes of administration.

In light of the above arguments, Applicants hereby request that the rejection be withdrawn.

**Conclusion**

Applicants again thank the Examiner for his careful review of the case. Based on the Remarks presented above, Applicants respectfully submit that Claims 1, 15-20, and 22-24 are now in condition for allowance. A Notice to this effect is respectfully requested.

Please charge any fees that may be associated with this matter, or credit any overpayments, to our Deposit Account No.: 03-1721.

Respectfully submitted,

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